or a salt or isomer thereof.

REMARKS

Entry of the foregoing amendments, reconsideration and re-examination of the subject application, as amended, pursuant to and consistent with 37 C.F.R. §1.112, and in light of the remarks which follow, are respectfully requested.

By the present amendments, the claims have been rewritten in order to expedite prosecution. In particular, the amendments and newly-submitted claims should overcome the previous §112 issues.

Turning now to the Office Action, Claims 28 through 37 were rejected under 35 U.S.C. §112, first paragraph, as assertedly not being enabled by the teachings of the subject application. The Office Action indicates that claims directed to treatment of various disorders are not enabled on the basis that the specification allegedly "fails to provide any evidence that any of the compounds to which the method claims are drawn will exhibit any particular activity in any given assay." This rejection is respectfully traversed. Contrary to the office Action, the specification does contain information which would allow one of ordinary skill to reasonably conclude that the claimed methods are efficacious. In particular, the specification describes, e.g., at page 1, that the compounds according to the invention have pronounced activity in the field of cell proliferation and differentiation, and therefore find application in topical and systemic treatment of various

disorders, including dermatological complaints. Moreover, at page 17 of the subject application, Applicants describe that compounds according to the invention show activity in established assays for evaluating differentiation, i.e., the mouse embryonic teratocarcinoma cell test (F9), which is described in *Cancer Research*, Vol. 43, page 5268, 1983, as well as in the test of inhibition of ornithine decarboxylase after induction with TPA in mice, which is described in *Cancer Research*, Vol. 38, pages 793-801, 1978. As described in the subject application, these are accepted assays for evaluating the activity of the subject compounds for effecting cell differentiation and cell proliferation, respectively. The F9 differentiation test evaluates agonist activity as retinoic acid receptors. In this assay, a compound which partially or totally inhibits the effect produced by a retinoid which is an agonist based on its effect on the secretion of plasminogen activator. Moreover, as discussed in the paragraph bridging pages 17-18 of the subject application, some of the compounds of the present invention are also active in a test which provides for the identification of molecules which are RAR antagonists. This information is contained in French Patent 95/07320, filed on June 19, 1995, by the same Assignee. Therefore, based on the foregoing, Applicants respectfully traverse the Examiner's assertion that there is no evidence in support of the claimed therapeutic methods.

Moreover, in further support of the claimed methods, Applicants further provide a list of references which provide evidence that retinoic acids have established utility for

the claimed methods of therapy. In particular, this list of references substantiates that retinoic compounds, such as are described in the subject application, may be used for the treatment of various skin diseases, i.e., acne, for promoting hair growth, for treatment of dry eye syndrome, for effecting inflammation and treatment of inflammatory disorders, for effecting depigmentation, for alleviating or preventing the effects the photo-irradiation of the skin, treatment of hyper-keratotic disorders, actinic keratosis, skin cancer, for promoting wound healing, for treating viral diseases such as AIDS, for treating arteriosclerosis and cardiovascular diseases, for treatment of cancer, and treatment of neurogenerative disorders.

In further support thereof, Applicants attach to this Reply copies of references further substantiating the known and acceptable usage of retinoids for treatment. Peck et al, *The Retinoids*, pages 631 to 659 is a review article relating to the use of synthetic retinoids for dermatological applications. It should be noted, in particular, that this reference describes the use of such compounds for treating of keratinization disorders, for use in treatment of cystic acne, psoriasis, cutaneous disorders of keratinization, and cancer. Further, Leyden et al, *J. American Academy Dermatology*, Vol. 15:901-914, 1986, describes the use of a retinoid compound for treatment of acne vulgaris. Also, Bazzano et al, *J. American Academy Dermatology*, Vol. 15:880-883, 1986, describes the use of a retinoid compound for promoting hair growth. Further, Lowe, *Practical Psoriasis Therapy*, Chapter 11, entitled "Synthetic Retinoids for Psoriasis", pages 111-

115, 1986, describes the use of retinoids specifically etretinate for treatment of various forms of psoriasis. Also, an Abstract by the Assignee of this application, entitled "Topical Retinoids for Warts and Keratoses in Transplant Recipients" describes the topical application of retinoids in transplant recipients receiving immunosuppressive therapy in order to prevent skin cancer, particularly squamous cell carcinomas, and for control of the proliferation of pre-malignant and malignant lesions in organ transplant recipients. Finally, Turpin et al, *Journal of Immunology*, Vol. 148:2539-2545, 1992, describes the use of retinoids for modulating the transcription of HIV gene expression. Moreover, in their conclusion, the authors note that there are increasing number of reports describing the use of vitamin A or other retinoids for the treatment of symptoms of HIV infection. Specifically, the reference indicates that such compounds are useful for treatment of Kaposi's sarcoma, lichen planus, papillomavirus infection and oral hairy leukoplakia in HIV infected individuals. Therefore, based on the foregoing and the attached references, Applicants respectfully submit that the claimed methods of treatment are adequately supported by the information contained in the subject application, coupled with numerous references supporting the conclusion that retinoids which affect cell proliferation and cell differentiation have accepted usage in the treatment of the recited condition. Therefore, withdrawal of the §112, first paragraph, rejection is respectfully requested.

Claims 28 through 37 stand rejected under 35 U.S.C. §112, second paragraph, as assertedly being indefinite. This rejection is respectfully traversed to the extent it may be applicable to the claims as amended. The objection with respect to Claim 28 should be moot in light of the present amendments. Specifically, the claim clarifies that at least one compound is administered, which finds substantial support in the as-filed disclosure. For example, at page 21, lines 23-26, the application indicates that the subject of the present invention is also medicinal compositions containing at least one compound of formula (I), as defined in the specification. Therefore, it would be clear that Applicants intended to claim usage of one or more compounds according to the invention. This would further be clear based on page 18, lines 16-18, wherein Applicants note that some of the compounds may provide synergism to the biological activity of products binding to nuclear receptors. Still further, at page 14, Applicants make clear that the cosmetic compositions according to the invention comprise at least one compound of formula (I) as defined in the subject application.

Also, the recitation of "geometrical isomer" is moot as this phrase is no longer contained in the claims. Also, the missing parenthesis noted by the Examiner with respect to R_1 has been corrected. Further, the objection to Claim 32 as to whether a single or multiple compounds is administered has been eliminated. The objection of Claims 31 to 33 has been corrected by the cancellation of these claims in favor of new Claims 38 through 41. The objection to Claim 34 with respect to antecedent basis has been obviated

because this claim is now dependent on claim 29, which clearly refers to dermatological conditions associated with differentiation or proliferation. Further, the objection to Claim 37 is moot based on the cancellation of this claim. Also, the objection to Claim 35 should be moot as this claim has been rewritten to overcome the antecedent basis rejection. Therefore, withdrawal of the §112, second paragraph, rejection of Claims 28 through 37 is respectfully requested.

Based on the foregoing, this application is believed to be in condition for allowance. A Notice to that effect is respectfully solicited. However, if any issues remain outstanding upon consideration of this Reply, the Examiner is respectfully requested to contact the undersigned so that prosecution may be expedited.

Respectfully submitted,

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Removed Ref on hair growth Bazzano, Gail et al

RETINOID APPLICATIONS

(References compiled by CIRD GALDERMA DOCUMENTATION 2.12.94)

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